

## Original Article

# Effect of glucomannan on functional constipation in children: a systematic review and meta-analysis of randomised controlled trials

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**Background and Objectives:** Constipation, a common complaint in children, considerably affects the quality of life. This systematic review assessed the treatment effects of glucomannan on children with constipation by summarising evidence from previous randomised controlled trials (RCTs). **Methods and Study Design:** A comprehensive electronic literature search was conducted for identifying eligible RCTs that evaluated the effectiveness of glucomannan. The results were reported as mean differences (MDs), standardised mean differences (SMDs), and risk ratios (RRs) with 95% confidence intervals (CIs). The primary outcome was the defecation frequency per week; the secondary outcomes were stool consistency and the rate of successful treatment. A meta-analysis was conducted using the random effects model. **Results:** Three RCTs evaluating 122 participants were identified. Glucomannan use was associated with an increased frequency of defecation (3 trials; MD=1.40; 95% CI: 0.36–2.44,  $p=0.008$ ); however, there were no significant differences in the outcomes of stool consistency (3 trials; SMD=0.48; 95% CI: -0.44 to 1.40,  $p=0.300$ ) or the rate of successful treatment (2 trials; RR=1.36; 95% CI: 0.48–3.81,  $p=0.110$ ). **Conclusions:** Glucomannan moderately increases the defecation frequency of children with constipation but is not associated with a reduction in stool consistency or overall improvement in the rate of successful treatment. However, these results should be cautiously interpreted because of the small sample size and the risk of products containing glucomannan need to be considered. Additional large-scale and well-designed RCTs are necessary to evaluate the efficacy and long-term safety of glucomannan.

**Key Words:** constipation, glucomannan, children, meta-analysis, RCTs

## INTRODUCTION

Constipation is a common, frustrating, and lasting disorder in children worldwide and significantly affects the quality of life, thus affecting both physical and emotional well-being of the children and their families.<sup>1</sup> Studies have reported that approximately 40% of these children are burdened by psychological problems, such as eating disorders, truancy, family problems, social isolation, and depression.<sup>2-6</sup> The reported prevalence of constipation in children varies from 0.7% to 29.6% based on the geographical areas of their residence.<sup>7</sup> Furthermore, constipation in children is characterised by infrequent, hard, and painful defecation as well as involuntary faeces loss.<sup>8,9</sup> Several mechanisms may underlie the pathogenesis of chronic constipation. The treatment can include health education, dietary advice, laxatives,<sup>10</sup> decompression, and surgery. In clinical settings, 36.4% of children with functional constipation may select other forms of alternative treatments.<sup>11</sup> However, none of the aforementioned treatments have revealed satisfactory effectiveness in clinical settings.<sup>12</sup>

Glucomannan is a soluble fibre derived from the tuber

of *Amorphophallus konjac*. The major chemical components of glucomannan are mannose and glucose sugars. From a nutritional science perspective, glucomannans have extremely low gut toxicity and can play crucial roles in metabolism and homeostasis maintenance. Therefore, glucomannans are now widely used in clinics as a supplementary treatment for diabetes and obesity.<sup>13</sup> For gastrointestinal diseases, because of its favourable function in metabolism maintenance, glucomannan is widely used as a natural laxative, increasing the stool volume without harming the colonic microecology.<sup>14</sup>

However, some observational studies investigating the benefit of glucomannan have reported heterogeneous re-

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Manuscript received 26 August 2015. Initial review completed 19 November 2015. Revision accepted 27 December 2015.

doi: 10.6133/apjcn.032016.03

sults, thus complicating the evaluation of the effectiveness of glucomannan. However, observational studies may include some bias that is difficult to adjust for in cohort studies. Therefore, in this systematic meta-analysis, we have explored the association between glucomannan use and different clinical measures by collating evidence from several randomised controlled trials (RCTs).

## MATERIALS AND METHODS

All pooled analyses are based on previously published studies, and thus, no ethical approval and informed consent were required.

### Literature search

Two reviewers (YH and LZ) searched PubMed, EMBASE, ScienceDirect, and Cochrane Library databases from their inception until August 2015. In PubMed and Cochrane Library, we used Medical Subject Heading (MeSH) terms and keywords; in EMBASE, we used Emtree terms and keywords; and in ScienceDirect, we only used keywords. The MeSH terms included (1-6)-alpha-glucomannan and constipation, and the Emtree terms included mannan and constipation. Furthermore, the keywords were 'glucomannan', '*Amorphophallus conjac*', 'konjac', 'konjac mannan', 'konnyaku', 'KGM', 'constipat', 'astriction', and 'dyschizia'. We also searched the reference lists of previous systematic reviews on the same topic to widen the scope of our search. We managed the obtained data in Excel files.

### Study identification

According to the Cochrane Handbook, we devised restriction criteria for study selection.<sup>15</sup> The study population was restricted to children with constipation diagnosed using the Rome criteria. The intervention of interest was defined as the random assignment of glucomannan compared with that of placebo (or other alternatives). The primary outcome of interest was the defecation frequency, and the secondary outcomes of interest comprised stool consistency and the rate of successful treatment. We only included RCTs in our review, and observational studies, experimental studies, reviews, and letters or comments were considered ineligible. We did not set any restrictions for study regions or timings, but we restricted the language to English; these criteria were used for selecting the eligible studies during title and abstract screening. The eligible studies were included in the full-text review. Specific reasons for excluding all ineligible studies have been provided. During full-text review, we read all studies by emphasising on the following factors: (1) numerical measures having clinical or epidemiological significance, (2) accessible full text in English, (3) poor study design that could not be accepted, and (4) violation of the fundamentals of biology or clinical knowledge. Furthermore, the eligible studies identified in the full-text review process were included in the systematic review and considered for meta-analysis only if they had relevant measures. Reasons similar to those provided for study exclusion in title and abstract screening were provided in the full-text review. Similar to title and abstract screening, full-text review was conducted independently by the authors. Disagreements during study

identification were resolved through discussions. The study identification and selection processes followed the flow chart presented by PRISMA.<sup>16</sup>

### Data extraction

Two authors (YH and LZ) independently extracted the data by using a self-designed data extraction form. The following data were extracted in this review: first author; publication year; patient numbers; patient characteristics; study design; glucomannan dosage, route, and duration; successful treatment rate; defecation frequency; and other secondary outcome. Disagreements between reviewers were resolved by discussion or by consulting a senior researcher.

### Quality assessment

We used the Jadad scale score for assessing the methodological quality of the included studies.<sup>17</sup> This scale comprises 3 items describing randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 point) in an RCT. A score of 1 was assigned to each aforementioned factor. An additional point was assigned when an appropriate method of randomization or blinding was selected, whereas a point was deducted on inappropriate selection. The quality scale ranged from 0 to 5 points. The studies were considered to be of a low and high quality if the Jadad scores were  $\leq 2$  and  $\geq 3$ , respectively.<sup>18</sup> Two independent reviewers performed the task, and any discrepancy was resolved by consulting senior researchers or through group discussions.

### Statistical analyses

First, we summarised the study characteristics in a table with clear footnotes and the corresponding signs. For the studies eligible for the meta-analysis, we used random effects models for calculating the pooled estimate because the studies were conducted in different countries, at different times, and with diverse study populations, which could introduce a high biological and methodological heterogeneity. Differences were measured as mean difference (MD) or standardised mean difference (SMD) with 95% confidence intervals (CIs) for continuous outcomes and risk ratios (RRs) with 95% CIs for dichotomous outcomes. Considering statistical heterogeneity, we used Cochran Q statistics, which follows the  $\chi^2$  distribution with  $n - 1$  degrees of freedom ( $n$  indicates the number of included studies). Furthermore, the statistical results indicated statistical heterogeneity if the  $p$  value, which was obtained using the  $\chi^2$  distribution-based test, was smaller than 0.05.  $I^2$  statistics was used as a quantitative measure of statistical inconsistency across different studies and was adopted for investigating the proportion of between-study variation among the total variance.  $I^2$  statistics of 25%–50%, 50%–<75%, and  $\geq 75\%$  were considered to indicate a low, moderate, and high statistical heterogeneity, respectively.<sup>19</sup> Moreover, sensitivity analyses was performed by omitting one study in each experimental turn for exploring the possible source that introduced statistical heterogeneity and for investigating the effect of a single trial on the overall pooled estimate. The sensitivity analyses were not conducted when the outcome was the rate of successful treatment because of the small sample

size. We did not investigate the existence of publication bias by using the funnel plot in our study because of the limited number of available trials. Forest plots and all statistical calculation were conducted in Revman 5.3.

## RESULTS

### Study identification and selection

We obtained 116 articles after searching the electronic databases (PubMed: 21, Embase: 39, ScienceDirect: 23, and Cochrane Library: 33). However, we did not find any additional eligible articles after searching the reference lists of previous reviews. Twelve studies were excluded because of duplicate reports, and 100 studies were excluded from the title- and abstract-screening process (unmatched population, 21; unmatched study design, 69; studies that included glucosamin in a multicomponent supplement, 10; unmatched outcome of interest, none; and unmatched language, none). The remaining 4 full-text articles were retrieved for further evaluation; one of them was excluded because it was a follow-up study of an already included study.<sup>20</sup> Finally, 3 RCTs with 122 participants were included in the present systematic review and meta-analysis.<sup>21-23</sup> The flow chart of study selection is presented in Figure 1.

### Study characteristics and quality

The key characteristics of the 3 studies, namely 2 parallel studies and 1 crossover study, included in the systematic review are outlined in Table 1. These studies were published in 2000, 2004, and 2011, including 19, 31, and 72 participants. All 3 RCTs reported baseline constipation frequency per week and stool consistency and treatment effects,<sup>21-23</sup> and 2 reported the rate of successful treatment.<sup>21,22</sup> Two studies<sup>21,22</sup> used maltodextrin as the comparison treatment, and one study<sup>23</sup> used placebo for comparison. Furthermore, the Jadad score of the included studies was 3–5 (median, 4), indicating an acceptable methodological quality; however, there might be some

other concerns regarding the methodology and effectiveness of the valuation process because of different glucosamin doses and different treatment allocation and placebo utilisation methods. Furthermore, there could be some selection bias introduced by the small sample size of the included trials. The small sample size could influence the precision of the statistical estimates by increasing the standard error. Moreover, among these trials, one included children with severe brain damage,<sup>23</sup> whereas another included patients with and without encopresis,<sup>21</sup> which could be another concern regarding the study generalizability. The scale used for evaluating the stool consistency has been mentioned in the 3 studies.<sup>21-23</sup>

### Primary outcome: defecation frequency

Overall, one study<sup>21</sup> revealed that the effectiveness of glucosamin, with respect to defecation, was not statistically significant, whereas the other two<sup>22,23</sup> studies reported that glucosamin significantly increased the defecation frequency. Based on the pooled average estimate, glucosamin was associated with an increased defecation frequency (MD=1.40, 95% CI: 0.36–2.44,  $p=0.008$ ; Figure 2). The  $p$  value derived from the Q statistics test revealed a moderate statistical heterogeneity ( $p=0.120$ ), and the test results were consistent with the  $I^2$  value (53%). The pooled point estimates substantially changed after excluding the results by Chmielewska et al.; however, the CI highly overlapped (MD=1.04, 95% CI: -0.83 to 2.90,  $p=0.28$ ) and  $I^2$  was 65%, indicating a moderate statistical heterogeneity. Similar results were observed after excluding the study by Staiano et al (MD=1.09, 95% CI: -0.55 to 2.73,  $p=0.19$ ), with a higher  $I^2$  value (75%). Furthermore, exclusion of the study by Loening-Baucke et al, which had a crossover design, yielded results similar to the pooled results of all the studies (MD=1.83, 95% CI: 1.20–2.47,  $p<0.0001$ ), and no evidence of statistical heterogeneity was observed ( $I^2 = 0.0\%$ ).

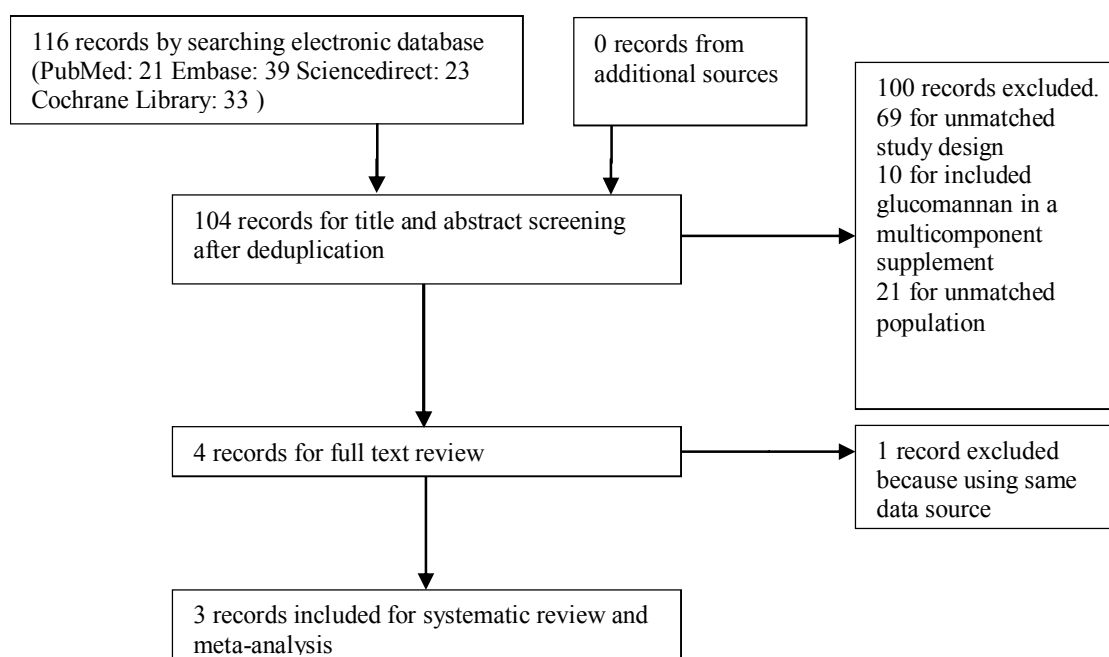


Figure 1. Flow diagram illustrating study selection for the meta-analysis.

**Table 1.** Characteristics of the studies included in the meta-analysis.

First author (year of publication)	No. of patients (glucomannan/ control)	Study design/ length of the trial	Jadad score	Patient characteristics	Glucomannan group	Control group	Standard of treatment success
Vera Loening- Baucke (2004) <sup>21</sup>	31 (20/11)	RCT, DB, crossover/ 4 weeks	4	Children aged 4.5–11.7 years with chronic functional consti- pation for $\geq 6$ months with or without encopresis	Glucomannan 100 mg/kg body weight daily (maxi- mum, 5 g/day), capsule, via po, 4 weeks	Maltodextrin	Successful treatment was rated by the physician and was defined as $\geq 3$ BMs/wk and $\leq 1$ soiling episode/3 wk with no abdominal pain
Anna Chmielewska (2011) <sup>22</sup>	72 (36/36)	RCT, DB, parallel/ 4 weeks	5	Children aged 3–16 years with functional constipation	Glucomannan 2.52 g/day, sachet, bid, via po, 4 weeks	Maltodextrin	Three or more BMs with no episodes of soiling during the last week of product consumption
Annamaria Staiano (2000) <sup>23</sup>	19 (9/10)	RCT, DB, parallel/ 12 weeks	3	Children aged $5.7 \pm 4.2$ years (mean $\pm$ SD) with severe brain damage, constipation for at least 12 months	Glucomannan 100 mg/kg body weight, bid, capsule, via po, 12 weeks	Placebo	Not mentioned

RCT: randomised controlled trial; DB: double blind; SD: standard deviation; BMs: bowel movements.

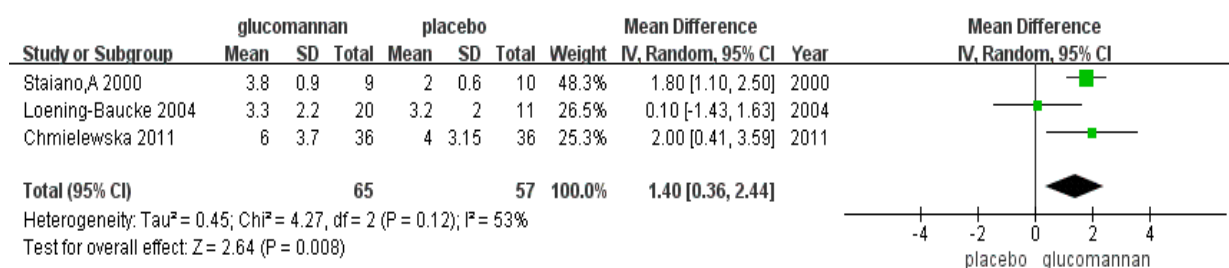


Figure 2. Meta-analysis for the weekly defecation frequency in children with constipation comparing glucosamin with placebo.

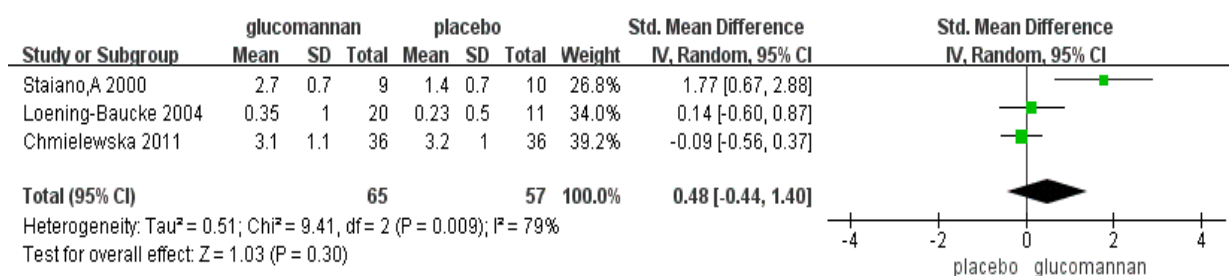


Figure 3. Meta-analysis of stool consistency in children with constipation comparing glucosamin with placebo

**Secondary outcomes: stool consistency and rate of successful treatment**

All 3 studies reported a change in stool consistency after treatment. However, only Staiano et al reported a statistically significant effectiveness of glucosamin that could increase the stool consistency. The pooled average estimate revealed no significant difference between the treatment and comparison groups with respect to stool consistency (SMD=0.48, 95% CI: -0.44 to 1.40, p=0.300; Figure 3). The Q statistics test demonstrated significant statistical heterogeneity (p=0.009), which was consistent with the obtained I<sup>2</sup> value (79%). Moreover, we conducted sensitivity analyses by omitting one trial in each experimental turn. Thus, we obtained 3 pooled estimates, all of which were similar considering the point estimates and CIs. Statistical heterogeneity was not observed after excluding the study by Staiano et al.

Two studies reported the percentage of successful treatment,<sup>21,22</sup> and both studies mentioned that the use of glucosamin was not associated with an increased rate of successful treatment. Therefore, the pooled results did not reveal any statistical significance (RR=1.36, 95% CI: 0.48-3.81, p=0.110, Figure 4). The Q statistic (p=0.110) and I<sup>2</sup> (60%) values revealed a moderate statistical heterogeneity among the studies (Figure 4).

**DISCUSSION**

Thus far, this is the first systematic review and meta-analysis to evaluate the effectiveness of glucosamin in ameliorating the symptoms of constipation in children. Our findings reveal that glucosamin may increase the frequency of defecation in children with constipation. Compared with the comparison groups, the treatment groups exhibited a decrease in the hardness of stools and increase in the rate of successful treatment. One previous systematic review and meta-analysis investigated the association between the dietary fibre consumption and risk of constipation based on clinical trials, and they concluded that a higher consumption of glucosamin could be associated with an increased defecation frequency in constipation among patients of all age groups;<sup>24</sup> these results support our findings.

Our sensitivity analyses suggested that Loening-Baucke et al might have introduced some heterogeneity in both methodological and statistical aspects. First, their study was a crossover trial, which had treatment allocation procedures different from those of the other 2 trials. Moreover, Loening-Baucke et al enrolled children with both constipation and encopresis,<sup>21</sup> thus introducing a systematic difference compared with the patients enrolled in the other 2 studies. Moreover, the glucosamin dosage

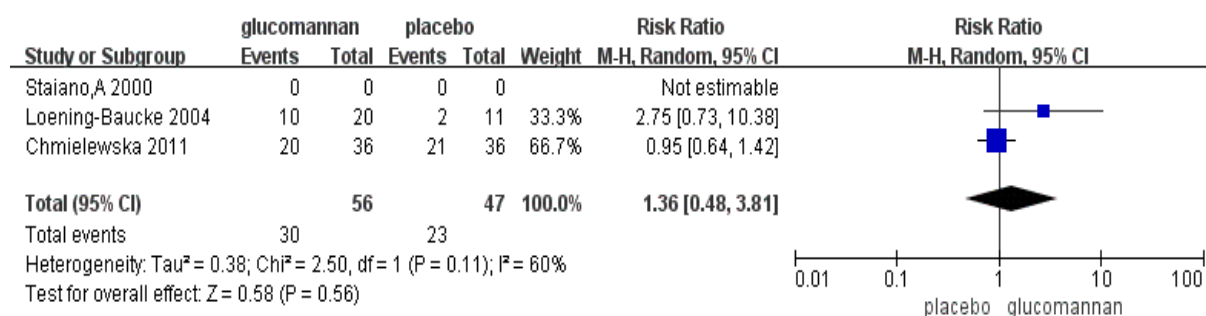


Figure 4. Meta-analysis for the rate of successful treatment in children with constipation comparing glucosamin with placebo.

assigned in this trial was lower than that assigned in the remaining 2 trials, which could be another crucial source of methodological heterogeneity. Our findings suggest that glucomannan had no effect on stool softening. Our results also revealed that glucomannan was not associated with an enhanced rate of successful treatment in children with constipation (RR: 1.36, 95% CI: 0.48–3.81,  $p=0.110$ ). However, these results are contradictory to our clinical observation, possibly because of the limited number of included studies, which increased the level of statistical heterogeneity. With respect to reporting the adverse effects, only one of the studies reported minor side effects, such as gastroenteritis, vomiting, bronchitis, otitis media, and pruritus; among these, only vomiting was considered associated with glucomannan. The overall rates of other adverse effects were similar in the treatment and comparison groups. Therefore, this observation implied a favourable safety level of glucomannan usage in clinical settings.

### **Strengths and limitations**

Our study has the following strengths. First, compared with the systematic review of observational studies, clinical trials avoid most selection bias by random treatment allocation and strict inclusion criteria. Thus, a systematic review and meta-analysis of RCTs is a more efficient manner of evaluating treatment effectiveness. Second, we performed several sensitivity analyses when pooling the results, which facilitated the discussion of the biology and methodology of the heterogeneity source. However, our study has the following limitations. First, the sample size was extremely small, thus complicating performing subgroup analysis based on some relevant study characteristics. Therefore, we could not investigate the publication bias. Second, the trials included in our review were conducted on a relatively small scale, thus compromising on the precision and representativeness and affecting the precision of the pooled estimate.

### **Conclusion**

Our systematic review and meta-analysis suggests that glucomannan may increase the frequency defecation among children with constipation but may not have such favourable effects on softening the stool and enhancing the successful treatment rate. Considering the substantial biological, methodological, and statistical heterogeneity among these trials, these results should be cautiously interpreted. Additional large-scale, well-designed RCTs on this topic are required. The effectiveness and side effects of long-term glucomannan use among children with constipation should be examined in the future in a more systematic manner.

### **Safety considerations**

On the basis of the limited studies, the most prevalent side effects of glucomannan are flatulence, diarrhoea, and abdominal discomfort.<sup>25</sup> Oesophageal obstruction resulting from the swelling of glucomannan tablets or hygroscopic medications containing glucomannan have been reported.<sup>26,27</sup> The US Food and Drug Administration issued a second warning of the danger of choking on the konjac candy after consulting with experts on choking

from the Consumer Product Safety Commission; the experts confirmed that the candy posed a high choking risk, particularly to infants, children, and the elderly.<sup>28</sup> In May 1985, marketing of glucomannan tablets was prohibited in Australia, and only the capsule and powder forms were available.<sup>26</sup> Health Canada advises the consumption of a glucomannan-containing product with at least 8 ounces of water or other fluids and not immediately before sleeping.<sup>29</sup> No relevant study has yet reported the long-term safety of glucomannan.

### **ACKNOWLEDGEMENTS**

We acknowledge the valuable suggestions provided by Professor Ping Han (Department of Nutrition and Food Hygiene of Zhengzhou University) during the design phase.

### **AUTHOR DISCLOSURES**

There are no conflicts of interest and funding disclosure.

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